Comparison of Cost-Effectiveness of Bronchodilator Drugs via Inhaler or Nebulizer Route in Exacerbations of Chronic Obstructive Pulmonary Disease

Cost-effectiveness of MDI/Spacer versus Nebulised System

Arzu Mirici, MD; Mehmet Meral, MD; Metin Akgün, MD; Hasan Kaynar, MD; Suat Kiriş, MD

Department of Chest Diseases, Atatürk University Faculty of Medicine, Erzurum, Turkey

Abstract

This study, which was designed as a prospective, randomized, double-dummy, parallel-group clinical trial, aimed to compare the use of inhaler and nebulizer delivery systems in bronchodilator treatment in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) from the viewpoints of effectiveness.

A total of 43 patients who had moderate to severe acute exacerbations of COPD and required hospitalization were enrolled in this study. The patients were randomized to take either an inhaler bronchodilator drug via an MDI/spacer (Group 1, n=21) as a combination of 1600 mcg salbutamol and 320 mcg ipratropium bromide daily and a nebulised placebo or to take a bronchodilator drug via a nebulizer (Group 2, n=22) as a combination of 10 mg salbutamol and 2 mg ipratropium bromide daily and a placebo via an MDI/spacer. Airway obstruction (peak expiratory flow rate [PEFR]) and gas exchange (arterial partial pressure of oxygen [PaO_2] and carbon dioxide [$PaCO_2$], pH and oxygen saturation [SaO_2]) were evaluated at 30 min, 6, 24 and 48 hours, and on day 10. Total costs and costs of bronchodilator treatments were calculated in both groups.

There were no significant differences between groups at baseline except pH value. In both groups, differences were significant for PEFR, PaO_2 and SaO_2 ($p<0.001$), but not for $PaCO_2$ and pH, in comparison with baseline values. Overall, there were no significant differences between groups for all parameters (PEFR, PaO_2, $PaCO_2$ and SaO_2), while bronchodilator treatments in Group 1 was 6 times as cheap as compared to Group 2 ($p<0.001$]). Total cost was also lower in Group 1 ($250 in Group 1 and $295 in Group 2, $p<0.05$).

The results indicate that treatment cost was lower in Group 1, although both types of treatment had equal effectiveness in the treatment of acute exacerbations of COPD.

Turkish Respiratory Journal, 2004;5:(3):169-74

Keywords: *bronchodilator treatment, MDI/spacer, nebulizer, cost-effectiveness, COPD*

Introduction

It is estimated that in the USA, more than 15 million individuals suffer from COPD and more than 12 million have chronic bronchitis (1). In 1993, it was also estimated that the economic burden of COPD was more than $15.5 billion and that more than one third of this sum was spent for hospitalization (2). In a more recent study, the direct and indirect costs of managing COPD was found to exceed 32 billion USD annually, and this health care burden has provoked vigorous efforts by major public health organizations to evaluate and improve quality of care for COPD (3). In the study by Miravitlles et al (4), it was shown

Corresponding Author: *Dr. Mehmet Meral*
Atatürk Üniversitesi Tıp Fakültesi Göğüs Hastalıkları AD, Erzurum, Türkiye
Phone : +90 (442) 316 63 33
Fax : +90 (442) 316 63 40
E-mail : mmeral@atauni.edu.tr

that patients with COPD have approximately two exacerbations in a year and exacerbations are the main cause of presenting to outpatient clinics and of hospitalization of these patients (5). The median cost of hospital stay due to COPD exacerbations in the United States was estimated through the analysis of a prospective cohort of 1016 patients to be $7100 (5). In another study, it was found that hospitalization expenses accounted for 40.4% of the cost of health care in patients with moderate COPD and 62.6% in patients with severe COPD (6). However, no estimation of costs pertaining to management of acute exacerbations was given in these reports.

Airway obstruction in patients with COPD is commonly associated with airway hyperreactivity which is usually reversible with bronchodilator treatment (7, 8). COPD exacerbations are associated with increased dyspnea, cough, increased sputum production and purulent sputum (9). Appropriate management of exacerbations (including bronchodilators, short term steroids and appropriate antibiotic treatments) was shown to decrease relapse rates, morbidity, mortality and economic burden caused by the disease (9-13). β_2-agonists and anticholinergics are the two main bronchodilator drugs used in treatments of patients with COPD (13).

This study aimed to compare the cost-effectiveness of bronchodilator drugs administered via a metered dose inhaler MDI/spacer or a jet nebulizer in hospitalized patients with COPD exacerbation.

Materials and Methods

Patients

All patients included in the study met the COPD diagnosis criteria based on the American Thoracic Society (ATS) guidelines (13). They were patients known to have a maximum ratio of FEV_1 / FVC <70% and a maximum FEV_1 <80% of predicted post-bronchodilator test before the exacerbations. At admission all had at least one of the following signs and symptoms: increased dyspnea, increased production and purulence of sputum that led to a change in treatment. Criteria for exclusion were the presence of other conditions such as cystic fibrosis, asthma, severe bronchiectasia, pneumonia, severe hypertension, and severe exacerbation requiring invasive or noninvasive mechanical ventilation. Patients who were not using the MDI/spacer with the appropriate technique were also not included the study.

Study design

The study protocol was approved by local ethics committee of the Medical Faculty.

The study was designed as a randomized, double-dummy and parallel group trial to be conducted between September 2000 and August 2002. The patients were assessed at baseline, at 30 minutes, 6 hrs, 24 hrs, 48 hrs following the initiation of the treatment and on the 10th day of the study. The patient was withdrawn from the study if acute respiratory acidosis or need for mechanical ventilation occurred. These patients received the necessary interventions. Randomization was performed using unmarked, ordered, sealed envelopes. No stratification method was used for randomization. The randomization order was determined using a computer generated list of random numbers.

Two treatment groups were constituted, to which eligible patients who had moderate or severe exacerbations of COPD were randomly allocated. MDI/spacer was used as the method of delivery of bronchodilator drugs in Group 1 and and jet nebulizer in patients in Group 2. Additional treatment including short term oral steroids, theophylline and/or antibiotics was given as required. Supplementary oxygen was used to maintain SaO_2 >90%.

Bronchodilator drugs were given as below:

In Group 1: 100 µg salbutamol and 20 µg ipratropium bromide per puff as a combined preparation 4x4 times daily (total daily doses of 1.6 mg salbutamol and 0.32 mg ipratropium bromide) via an MDI/spacer and a placebo nebulised suspension via a jet nebulizer.

In Group 2: 2.5 mg salbutamol and 500 µg ipratropium bromide per nebulizer ampoule 4 times daily (total daily doses of 10 mg salbutamol and 2 mg ipratropium bromide) via a jet nebulizer and a placebo via an MDI/spacer.

All patients were hospitalized after initial evaluation. Baseline values of Peak Expiratory Flow Rate (PEFR) and/or Force Expiratory Volume in one-second (FEV_1), Force Vital Capacity (FVC), and arterial blood samples were recorded. PEFR measurements were used in the analysis, because FEV_1 measurements after hospitalization were not available for all patients. Baseline pulmonary function measurements were performed by a computerized spirometer (Sensor Medics, Vmax 22) according to the ATS criteria. After hospitalization, PEFR measurements were performed three times and the best one was accepted. The % predicted PEFR values were calculated according to the directions of the manufacturer firm, taking into account the normal values for sex, age and height. Arterial blood samples were taken by a catheter inserted in the brachial artery and analyzed for PaO_2, $PaCO_2$, SaO_2 and pH. Pulmonary function assessment and arterial blood analyses were done at 30 minutes, 6, 24 and 48 hours and on day 10. Patients were inspiring room air at baseline and on day 10, but were on supplementary oxygen at 30 minutes, 6, 24 and 48 hours.

Cost analysis

At the end of the study, the total cost of the treatment including laboratory investigations and cost of bronchodilator therapy were calculated for each group separately. In the nebulizer group, the total cost evaluation also included the cost of use of equipment. Ratio of cost of bronchodilator therapy to total cost was also calculated for the two groups.

Statistical analyses

Pearson Chi-square and Mann-Whitney tests were used in the comparison of baseline values between groups. Comparison of parameters between and in groups were done by repeated measures analysis of variance test. Evaluation of variations of every step of assessment according to baseline values was done using the Mann-Whitney test. The data were analyzed by SPSS version 9.0 (SPSS Inc.). Mean values for each step and 95% CIs in each group were calculated. The value of $p<0.05$ was accepted as significant.

Results

A total of 48 patients were randomized, from which 24 were randomly assigned to Group 1 and 24 to Group 2. Three patients in Group 1 and two patients in Group 2 were excluded from the study because of development of pneumothorax and pneumonia in Group 1 and of required mechanical ventilation in Group 2. Demographic characteristics and baseline values of the groups are shown in Table I. The pH values were not considered in the final statistical analysis, because pH baseline values were significantly different between the two groups ($p<0.05$).

Table 1. Comparison of baseline characteristics of two groups

	Group 1	Group 2	p-value
Mean age (years)	68.25	64.29	0.49
Sex (F/M)	7/14	6/16	0.11
Baseline PEFR (%)	39.58	32.57	0.13
Baseline PaO_2 (mmHg)	46.51	46.83	0.61
Baseline $PaCO_2$ (mmHg)	40.90	45.80	0.50
Baseline SaO_2 (%)	80.16	77.56	0.60
Baseline pH	7.417	7.341	0.02*

$PaCO_2$ = arterial partial pressure of carbon dioxide; **PaO_2** = arterial partial pressure of oxygen; **PEFR** = peak expiratory flow rate; **SaO_2** = arterial oxygen saturation ; **F** = female; **M** = male

In each group, it was found that increases in PEFR, PaO_2, SaO2 values within the groups were statistically significant ($p<0.001$ for all parameters). Changes in $PaCO_2$ values in each group were not statistically significant ($p=0.13$). Mean values for all parameters during the study are summarized in Table II.

In a comparison between groups, it was found that there were no significant differences between percentage changes in PEFR, PaO_2, $PaCO_2$ and SaO_2 values at the end of the study ($p=0.52$, $p=1.0$, $p= 1.0$, and $p=1.0$ for PEFR, PaO_2, $PaCO_2$, and SaO_2 respectively) (Figures 1-4).

Mean total cost of treatment was $250 per patient in Group 1 and $295 in Group 2 ($p<0.05$). The ratio of bronchodilator treatment cost to total cost was 3% in Group 1 and 15% in Group 2 ($p<0.005$) (Figure 5). Thus, the cost of bronchodilator treatment was 6 times cheaper in Group 1 than Group 2.

Table 2. Mean values in the groups at different follow-up times

Parameter	Baseline	30 min	6h	24h	48h	Day 10
PEFR (%)						
Group 1	39.58	38.83	44.08	50.42	55.83	60.58
Group 2	32.57	37.10	37.81	41.57	44.86	50.43
PaO_2 (mmHg)						
Group 1	46.51	57.85	59.63	57.42	60.32	58.05
Group 2	46.84	55.26	55.66	55.81	63.04	67.14
$PaCO_2$(mmHg)						
Group 1	40.90	41.60	40.13	40.53	41.89	41.28
Group 2	45.81	42.90	43.73	43.56	43.97	42.49
SaO_2 (%)						
Group 1	80.16	85.42	87.67	88.57	90.97	87.72
Group 2	77.57	84.34	86.36	86.05	89.14	91.85
pH						
Group 1	7.417	7.400	7.410	7.391	7.406	7.385
Group 2	7.341	7.386	7.385	7.374	7.391	7.391

$PaCO_2$ = arterial partial pressure of carbon dioxide; **PaO_2** = arterial partial pressure of oxygen; **PEFR** = peak expiratory flow rate; **SaO_2** = arterial oxygen saturation

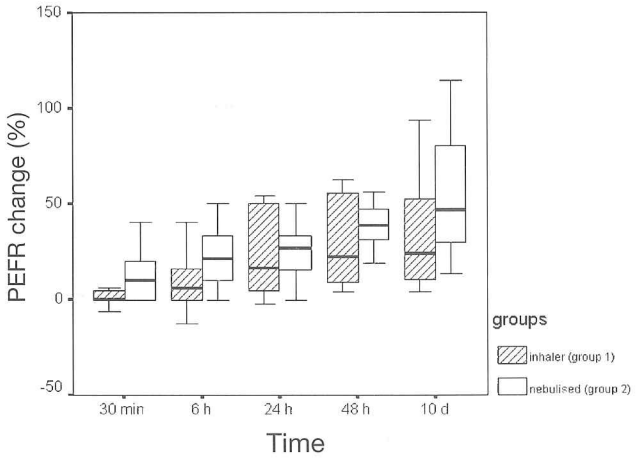

Figure 1. *Peak expiratory flow rate (PEFR): mean values, 95% CIs, minimum and maximum values (whiskers) for the two groups (MDI/spacer [Group 1] and nebulizer [Group 2]). In a comparison between groups, the differences in percentage change versus baseline values were not significant at 24 and 48 hours ($p=0.39$ and $p=0.21$, but were significant at 30 minutes, 6 hours and 10 days ($p=0.01$, $p=0.01$ and $p=0.03$). However, in the final evaluation, there were not significant differences ($p=0.52$).*

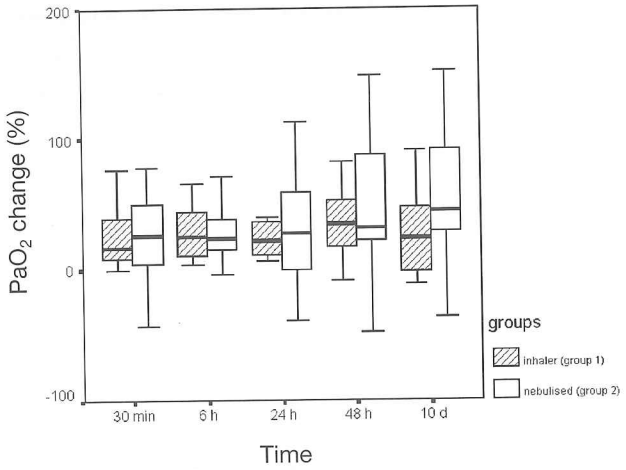

Figure 2. *Arterial partial pressure of oxygen (PaO_2): mean values, 95% CIs, minimum and maximum values (whiskers) for the two groups (MDI/spacer [Group 1] and nebulizer [Group 2]). In a comparison between groups, the differences in percentage change versus baseline values were not significant at 30 minutes, 6, 24 and 48 hours (p=0.78, p=0.94, p=0.88 and p=0.50), but were significant at 10 days (p=0.05). Overall, there were no significant differences (p=1.00).*

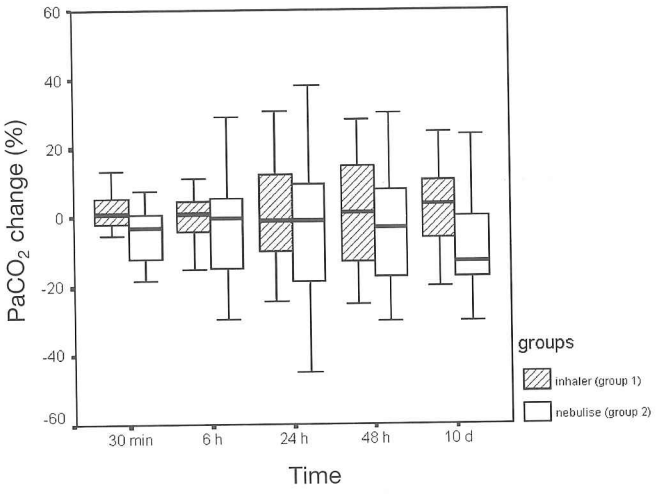

Figure 3. *Arterial partial pressure of carbon dioxide ($PaCO_2$): mean values, 95%CIs, minimum and maximum values (whiskers) for the two groups (MDI /spacer [Group 1] and nebulizer [Group 2]). In a comparison between groups, the differences in percentage change versus baseline values were not significant at 6, 24 and 48 hours and 10 days (p=0.91, p=0.45, p=0.31 and p=0.07), but were significant at 30 minutes (p=0.05). Overall, there were no significant differences (p=1.00).*

Discussion

In our study, although the effectiveness of two types of bronchodilator drug delivery was not significantly different, the cost of bronchodilator treatment was 6 times as expensive in Group 2. In comparing the two groups, although changes % in PEFR% values were better at 30 minutes (p=0.015), 6 hours (p= 0.014) and on day 10 (p= 0.039) in Group 2, the overall differences at the end of the study were not statistically significant (p=0.52) (Figure 1). The same was true for SaO_2. Although the values at 10 days were better in Group 2 than Group 1, the overall differences were not statistically significant (p=1.00) (Figure 4).

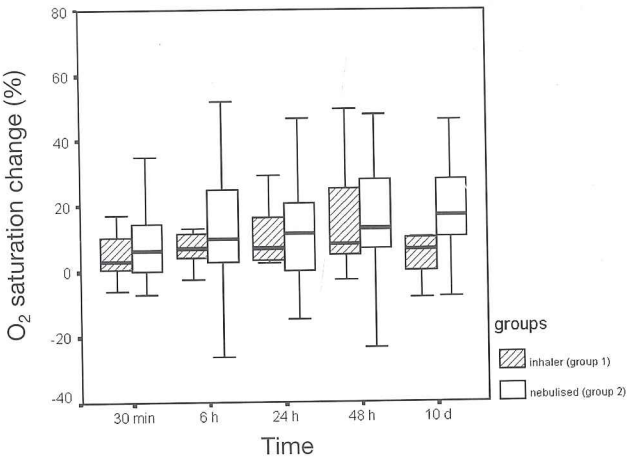

Figure 4. *Arterial oxygen saturation (SaO_2): mean values, 95% CIs, minimum and maximum values (whiskers) for the two groups (MDI/spacer [Group 1] and nebulizer [Group 2]). In a comparison between groups, the differences in percentage change versus baseline values were not significant at 30 minutes, 6, 24 and 48 hours (p=0.52, p=0.68, p=0.88 and p=0.62), but were significant at 10 days (p=0.03). Overall, there were no significant differences (p=1.00).*

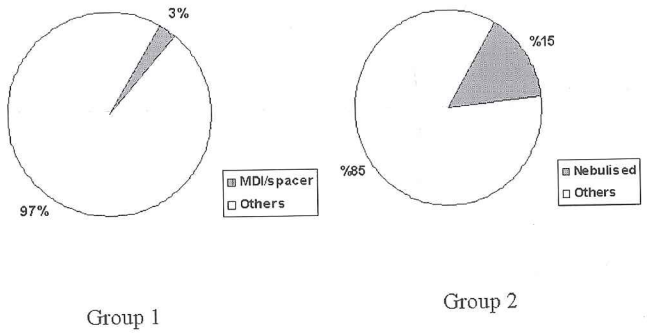

Figure 5. *Proportions of costs of bronchodilator treatments in the two groups. In Group 1, the ratio of cost of bronchodilator treatment to total cost was 3%. This ratio was 15 % in Group 2, (p< 0.005).*

COPD is a great economic burden in developed countries (1). In developing countries where tobacco consumption is high, the economic burden is becoming even a greater problem. In some studies, it was reported that hospitalization costs constituted 40-57% of the total cost of treatment in patients with COPD (6,15,16). There are some differences of opinion regarding selection of bronchodilator drug delivery methods in COPD exacerbations. In ERS (European Respiratory Society) and BTS (British Thoracic Society) guidelines, it is recommended that bronchodilator drugs may be used via nebulizer; while MDI/spacer is recommended in ATS guidelines (17). In exacerbations of COPD, inhaled β_2 agonists should be given in as short a time as possible (18). These agents may be given via an MDI/spacer effectively if the patients are well instructed to use the proper technique. The anticholinergics

can also be given via nebulizer system or MDI (18). Use of a combination such as ipratropium-albuterol may simplify the medication regimen, thereby improving compliance (18) $ß_2$ agonists given via MDIs have a similar efficacy as the nebulizer system in COPD exacerbations (19).

In another study, 40 patients who had been mechanically ventilated and who required bronchodilator treatment had been randomized and classified to three groups as MDI/Spacer, nebulizer and in-line MDI (20). Albuterol levels in the urine had been measured in these 3 groups and its bioavailability had been evaluated after six hours. It was found that bioavailability values for MDI/spacer, nebulizer and in-line MDI were 38%, 16% and 9% respectively (p=0.02).

Nebulization has been the preferred method for administering bronchodilators to very young patients or to those patients who were unable to coordinate their inhalation due to agitation or severe obstruction (21). However, in routine clinical situations, bronchodilation equivalent to that of nebulization can be achieved with high doses of a bronchodilator delivered by an MDI fitted with a spacer (22-24).

While the effectiveness of nebulization is widely recognized, the method nevertheless has several disadvantages. Some studies indicate that nebulization can be inefficient in delivering aerosol medication (25,26). Compared to an MDI/spacer combination, a nebulizer dispenses more medication but without added therapeutic benefit. The potential for excess drug exposure is of concern since the inhalation of $ß_2$ agonists in high doses can cause nonpulmonary adverse effects such as tremor and anxiety (25). The cost of nebulization, which includes purchasing and maintainance costs, is greater than that of MDI/spacer (27). Power requirements, higher drug dosing, and costs of maintaining nebulizers and their peripheral equipment can be quite a burden for some patients (28).

Analysis of arterial blood gases is very important in assessing respiratory failure as well as the efficacy of oxygen therapy, and of mechanical ventilation during COPD exacerbations. In our study population, especially in Group 2, the baseline oxygen saturation values were very low, although the difference was not significant. These values indicate that there was severe respiratory failure in the patients. In one study, it was reported that at a pH value <7.30-7.35 or PaO_2<50 mmHg, intensive care unit (ICU) admission may be required, but in contrast, noninvasive or invasive mechanical ventilation support does not improve outcome when the pH is ≥7.35 (29). In our study population, pH baseline values were 7.41 and 7.34 in Group 1 and 2, respectively. On the other hand, according to "The Global Initiative for Chronic Obstructive Pulmonary Disease", admission to an intensive care unit should be considered when "severe dyspnea does not substantially respond to initial treatment, when the patient is in a state of confusion-lethargy-coma, or in persistent or worsening hypoxemia (PaO_2 < 50 mmHg) despite supplemental oxygen" (30). Our study population did not meet these criteria. As seen in Table II, measurements of the arterial blood gases at different times following treatment showed substantial improvement.

Based on the results of this study, it was concluded that an MDI/spacer, when the patient can apply an adequate technique, can be successfully used to deliver bronchodilator drugs, and that it has an important cost advantage and a similar efficacy as the use of a nebulizer. The use of an MDI/spacer should be given serious consideration as a treatment vehicle of choice in the management of COPD exacerbations.

Acknowledgement

This study was fully supported by the Faculty of Medicine without any support from any medical firm or research company.

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